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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Alexandre HUBOUX

Confirmation No. 8745

Application No.: 10/820,709

Group Art Unit: 1625

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Examiner:

For: PROCESS FOR THE OPTICAL RESOLUTION OF A PRECURSOR OF SCLAREOLIDE

Attorney Docket No.: 81455-5730

**SUBMISSION OF CERTIFIED PRIORITY DOCUMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicants have claimed priority of application no. PCT/IB02/03055 filed July 31, 2002, under 35 U.S.C. § 119. In support of this claim, a certified copy of said application is submitted herewith.

No fee or certification is believed to be due for this submission. Should any fees be required, however, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814.

Respectfully submitted,

Date 12/6/04

Allan A. Fanucci 30,256
(Reg. No.)

**WINSTON & STRAWN**
**CUSTOMER NO. 28765**

(212) 294-3311

Enclosures

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34, chemin des Colombettes, Case postale 18, CH-1211 Genève 20 (Suisse)
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# PATENT COOPERATION TREATY (PCT)
# TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

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International Application No. / Demande internationale n° PCT/IB02/03055

International Filing Date / Date du dépôt international 31 JULY 2002 (31.07.02)

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Geneva/Genève, 07 APRIL 2004 (07.04.04)

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**PCT REQUEST**

5730-PCT

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| 0 | **For receiving Office use only** | |
| 0-1 | International Application No. | PCT / IB 0 2 / 0 3 0 5 5 |
| 0-2 | International Filing Date | 31 JULY 2002 (31.07.02) |
| 0-3 | Name of receiving Office and "PCT International Application" | INTERNATIONAL BUREAU OF WIPO<br>PCT International Application |
| 0-4 | **Form - PCT/RO/101 PCT Request** | |
| 0-4-1 | Prepared using | PCT-EASY Version 2.92<br>(updated 01.06.2002) |
| 0-5 | **Petition**<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| 0-6 | **Receiving Office (specified by the applicant)** | International Bureau of the World Intellectual Property Organization (RO/IB) |
| 0-7 | **Applicant's or agent's file reference** | 5730-PCT |
| I | **Title of invention** | A PROCESS FOR THE RESOLUTION OF SCLAREOLIDE |
| II | **Applicant** | |
| II-1 | This person is: | applicant only |
| II-2 | Applicant for | all designated States except US |
| II-4 | Name | FIRMENICH SA |
| II-5 | Address: | P. O. Box 239<br>1, route des Jeunes<br>CH-1211 GENEVA 8<br>Switzerland |
| II-6 | State of nationality | CH |
| II-7 | State of residence | CH |
| II-8 | Telephone No. | +41 22 780 22 11 |
| II-9 | Facsimile No. | +41 22 780 33 38 |
| II-10 | e-mail | brigitte.dumas@firmenich.ch |
| III-1 | **Applicant and/or inventor** | |
| III-1-1 | This person is: | applicant and inventor |
| III-1-2 | Applicant for | US only |
| III-1-4 | Name (LAST, First) | HUBOUX, Alexandre |
| III-1-5 | Address: | 299, Mail des Allobroges<br>F-74370 PRINGY<br>France |
| III-1-6 | State of nationality | CH |
| III-1-7 | State of residence | FR |

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| IV-1 | **Agent or common representative; or address for correspondence**<br>The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent |
| IV-1-1 | Name (LAST, First) | SALVATERRA-GARCIA, Maria de Lurdes |
| IV-1-2 | Address: | FIRMENICH SA<br>1, route des Jeunes<br>P. O. Box 239<br>CH-1211 GENEVA 8<br>Switzerland |
| IV-1-3 | Telephone No. | +41 22 780 2211 |
| IV-1-4 | Facsimile No. | +41 22 780 3338 |
| V | **Designation of States** | |
| V-1 | Regional Patent<br>(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT<br>EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT<br>EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT<br>OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT |
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| V-5 | **Precautionary Designation Statement**<br>In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. | | |
| V-6 | **Exclusion(s) from precautionary designations** | NONE | |
| VI | **Priority claim** | NONE | |
| VII-1 | **International Searching Authority Chosen** | European Patent Office (EPO) (ISA/EP) | |
| VIII | **Declarations** | Number of declarations | |
| VIII-1 | Declaration as to the identity of the inventor | – | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | – | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | – | |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | – | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | – | |
| IX | **Check list** | number of sheets | electronic file(s) attached |
| IX-1 | Request (including declaration sheets) | 4 | – |
| IX-2 | Description | 6 | – |
| IX-3 | Claims | 1 | – |
| IX-4 | Abstract | 1 | EZABST00.TXT |
| IX-5 | Drawings | 0 | – |
| IX-7 | TOTAL | 12 | |
| | **Accompanying items** | paper document(s) attached | electronic file(s) attached |
| IX-8 | Fee calculation sheet | ✓ | – |
| IX-17 | PCT-EASY diskette | – | Diskette |
| IX-19 | **Figure of the drawings which should accompany the abstract** | | |
| IX-20 | **Language of filing of the international application** | English | |
| X-1 | **Signature of applicant, agent or common representative** | | |
| X-1-1 | Name (LAST, First) | SALVATERRA-GARCIA, Maria de Lurdes | |

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| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
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| 10-5 | International Searching Authority | ISA/EP |
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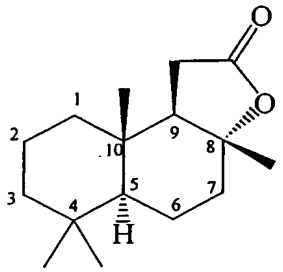
# A PROCESS FOR THE RESOLUTION OF SCLAREOLIDE

## Technical field

The present invention relates to the field of organic synthesis and more particularly to a new process to obtain (+)-(8R)-8,12-epoxy-13,14,15,16-tetranorlabdan-12-one, of formula




(I)

also known as (+)-sclareolide, starting from the racemic (±)-8,12-epoxy-13,14,15,16-tetranorlabdan-12-one, also known as sclareolide.

Said process is characterized by an enantiomeric or optical resolution using, as resolving agent, an enantiomer of the 2-(methylamino)-1-phenyl-1-propanol, also known as pseudoephedrine.

## Prior art

Despite the fact that (+)-sclareolide is an important intermediate for the synthesis of (-)-Ambrox®, which is an important perfumery ingredient, only few processes for the preparation of the compound of formula (I) have been reported in the prior art.

In EP 550 889 is reported a process for the optical resolution of sclareolide wherein an 1-(aryl)ethylamine is used as resolving agent. For the same process, Koga *et al.* in Tetrahedron Asymmetry, (**1998**), 9, 3819, report the use as resolving agent of some 1,2- or 1,3-amino-alcohols in addition to the previously cited 1-(aryl)ethylamine.

All the prior art procedures suffer from the disadvantages of needing complex procedures implying slow or complicated crystallization procedures and/or a re-crystallization. Additionally, low yields of the final product are frequently, if not always, observed.

Therefore, there is a need for a process capable of providing (+)-sclareolide from sclareolide and being of improved efficiency.

**Description of the invention**

In order to overcome the disadvantages of the prior art processes mentioned hereinabove, the present invention relates to a new highly efficient process for the isolation of (+)-sclareolide from sclareolide, characterized in that said process comprises the following reaction steps:

a) the hydrolysis of sclareolide into a corresponding hydroxy derivative,

b) treating, in a solvent, the hydroxy derivative with a pseudoephedrine enantiomer in order to obtain a biphasic system, wherein each phase comprises a majority of one enantiomer of the hydroxy derivative, and

c) treating the phase comprising a majority of the hydroxy derivative (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid in order to convert the latter into (+)-sclareolide.

Another object of the present invention concerns also the use of a pseudoephedrine enantiomer for the optical resolution of sclareolide.

In the first step the sclareolide is hydrolyzed into a hydroxy derivative which is susceptible of being optically resolved. As hydroxy derivative it is meant the hydroxy-acid, namely (±)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid, or an alkaline salt thereof, such as the $Na^+$, $K^+$ or $Li^+$ salt, preferably the $Na^+$ salt.

The hydrolysis may be performed according to any current method described in the prior art, e.g. as described by Koga *et al.* in Tetrahedron Asymmetry, (**1998**), 9, 3819 or by Goro *et al.* in EP 550 889. In general, the hydrolysis is performed by treating the sclareolide with an alkaline base, such as NaOH, KOH or LiOH, in an alcoholic solvent, such as methanol or ethanol, to obtain the corresponding alkaline salt of (±)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid. If desired, said alkaline salt may be transformed into the corresponding hydroxy-acid by treating the former with an acid, preferably a strong inorganic acid such as HCl, $H_2SO_4$, $HNaSO_4$, $HKSO_4$,$HNO_3$, $H_3PO_4$, $HPF_6$, $HBF_4$, para-toluenesulphonic acid (TsOH), benzenesulphonic acid, methanesulphonic acid or the

similar. The acid can be added in amounts comprised between 0.95 and 1.05 equivalent of protons per carboxylate function.

The second step of the invention process is the one allowing the separation of the two enantiomers of sclareolide. The principle of the present optical resolution is based on the solubility difference of the diastereomeric salts obtained by the reaction between the pseudoephedrine enantiomer and the two enantiomers of the hydroxy derivative obtained in step a). It is therefore possible to obtain a biphasic system wherein each phase comprises a majority of one enantiomer of the hydroxy derivative. Preferably the biphasic system consists in a solid phase, or precipitate, and a liquid phase, or liquor.

By "a majority of one enantiomer" we mean here at least 60%, preferably at least 75%, of an enantiomer of the hydroxy derivative; more preferably each phase will comprise at least 95%, or even 97.5%, of an enantiomer of the hydroxy derivative

The optical resolution is carried out in a solvent which is able to solubilize a majority of one of diastereomeric salt only, thus allowing the formation of the biphasic system. Examples of such solvents are aromatic solvents, petroleum fractions, halogenated solvents, ethers, esters, $C_4$-$C_{10}$ alcohols or mixtures thereof. Said solvents may be anhydrous or contain water up to saturation. Preferably, the solvent is selected from the group consisting of anhydrous tetrahydrofuran, toluene, xylene, benzene or cyclohexane.

As previously mentioned, as resolving agent is used a pseudoephedrine enantiomer, the latter may be the (1S,2S) or the (1R,2R)-2-(methylamino)-1-phenyl-1-propanol. The enantiomeric purity, or enantiomeric excess (e.e.), of the pseudoephedrine enantiomer used will influence the efficiency of the invention process, the higher will be the e.e. the most efficient will be the optical resolution of sclareolide. Preferably the pseudoephedrine enantiomer will have an e.e. higher than 95 %, more preferably higher than 98%.

The pseudoephedrine enantiomer can be used in the form of a free base or an acid salt, depending on the nature of the hydroxy derivative. If the latter is the hydroxy acid, the pseudoephedrine enantiomer is used as a free base. Alternatively if the hydroxy derivative is an alkaline salt then the pseudoephedrine enantiomer is used as an acid salt. The acid salt of the pseudoephedrine enantiomer may be added to the solvent as a

preformed salt or may be generated in situ by the addition of the free base and then an acid, in a quantity of about one equivalent of protons per free base. Suitable acids are HCl, $H_2SO_4$, $HNaSO_4$, $HKSO_4$,$HNO_3$, $H_3PO_4$, $HPF_6$, $HBF_4$, para-toluenesulphonic acid (TsOH), benzenesulphonic acid, methanesulphonic acid or the similar.

The pseudoephedrine enantiomer may be added in amounts comprised between 0.35 and 1.2 molar equivalent with respect to the product obtained in step a), preferably between 0.5 and 1.0 equivalents, even more preferably between 0.6 and 0.8 equivalents.

It has been found that when the (1R,2R)-pseudoephedrine is used then the precipitate comprises a majority of (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid, and the liquor comprises a majority of the other enantiomer of the hydroxy derivative. Vice versa when the (1S,2S)-pseudoephedrine is used, the liquor comprises a majority of (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid, and the precipitate comprise a majority of the other enantiomer of the hydroxy derivative.

For practical reasons, the use of (1R,2R)-pseudoephedrine in the invention process is more preferred.

The last step of the invention process allows to convert the (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid into (+)-sclareolide. This step may be performed according to any standard method for the generation of a lactone from a hydroxy-acid or salt thereof. In general, the conversion into the (+)-sclareolide is performed by treating the phase comprising a majority of (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid, obtained in step b), with a strong mineral acid, such as HCl, $H_2SO_4$, $HNaSO_4$, $HKSO_4$,$HNO_3$, $H_3PO_4$, $HPF_6$, $HBF_4$, para-toluenesulphonic acid (TsOH), benzenesulphonic acid, methanesulphonic acid or the similar, to recover the free (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid. Subsequently, the latter is treated with a catalytic acid, preferably acetic or propionic acid. The strong mineral acid is used in amounts comprised between 0.95 and 1.05 equivalent of proton in respect to the hydroxy acid, and the catalytic acid preferably in amounts comprised between 1% and 15%, preferably between 3% and 10%, molar equivalent in respect of the hydroxy acid.

This reaction step is carried out in the presence of a solvent. Non-limiting examples of such a solvent include aromatic solvents such as benzene, toluene or xylene, hydrocarbon solvents such as cyclohexane, ethers or mixtures thereof. However aromatic

solvents are preferred. During the formation of the (+)-sclareolide it may be useful to remove the water which is formed, e.g. by azeotropic distillation.

The temperature at which the conversion of the free (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid into (+)-sclareolide may be carried out is comprised between 60°C and 150°C, preferably between 95°C and 125°C.

A process according to the invention allows to isolate (+)-sclareolide from the racemic sclareolide in high yields, high e.e. and, in general, without any re-crystallization or complex procedure, to the contrary of what is described in the prior art. Typical yields of the invention process are in the range of 80%, based on the amount of (+)-sclareolide present in the starting racemic sclareolide, or even, e.g., more than 90%. Typical e.e. of (+)-sclareolide obtained at the end of the invention process are higher than 50%, but preferably higher than 90% or even 95%. Such results are quite unexpected in view of the above-cited prior art.

The invention will now be described in further details by way of the following examples, wherein the abbreviations have the usual meaning in the art, the temperatures are indicated in degrees centigrade (°C); $^{1}$H-NMR spectral data were recorded at 400MHz and $^{13}$C NMR spectra were recorded at 100 MHz in DMSO, the chemical displacements δ are indicated in ppm with respect to the TMS as standard, the coupling constants J are expressed in Hz and all the abbreviations have the usual meaning in the art.

## Example 1

### Preparation of (1R,2R)-1-hydroxy-N-methyl-1-phenyl-2-propanaminium (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oate

In a 2 liter, three-necked, round-bottomed flask equipped with a reflux condenser, a mechanical stirrer and containing 1.0 l of tetrahydrofuran (THF) were introduced 268.4 g (1.00 mole) of (±)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid (obtained according to EP 550889) and 119.8 g (0.725 mole) of (1R, 2R)-pseudoephedrine. The resulting suspension was heated to reflux for 1 hour and the temperature was then gradually

lowered to room temperature over 2 h 30 min. The suspension was filtered and the precipitate washed twice with 250 ml of THF. The resulting solid was dried under vacuum to give 199.1 g (0.459 mole, yield = 92%) of the title salt.

$^1$H-NMR:7.35-7.23 (m, 5H, Ph-**H**); 4.28 (d, 1H, J = 7.6 Hz, C**H**(OH)); 2.69 (dq, J = 7.6 and 6.6 Hz, 1H, C**H**($NH_2(CH_3)$)); 2.36 (s, 3H, $NH_2C\mathbf{H}_3$); 2.33 (dd, J = 16, 4.2 Hz, 1H, C**H**COO); 2.02 (dd, J = 16, 6.3 Hz, 1 H, C**H**COO); 1.75 (dd, J = 6.3 4.2 Hz, 1H, C**H**(CH2)COO); 1.72-1.03 (m, 10H, $5C\mathbf{H}_2$); 0.96 (s, 3H, $C\mathbf{H}_3CH(OH)$); 0.91 (m, 1H, $CHC(CH_3)_2$); 0.84 (s, 3H, $C(C\mathbf{H}_3)_2$); 0.76 (s, 3H, $C(C\mathbf{H}_3)_2$); 0.75 (d, J = 6.6 Hz, 3H, $C\mathbf{H}_3CHNH_2(CH_3)$); 0.73 (s, 3H, $CC\mathbf{H}_3$).

$^{13}$C-NMR: 176.6 (s); 143.1 (s); 127.8 (d); 127.1 (d); 127.0 (d); 75.6 (d); 70.9 (s); 60.2 (d); 56.3 (d); 55.5 (d); 43.7 (t); 41.4 (t); 38.57 (s); 37.9 (t); 33.2 (q); 32.8 (s); 32.5 (q); 30.5 (t); 24.0 (q); 21.3 (q); 19.9 (t); 17.9 (t); 14.9 (q); 14.4 (q).

## Example 2

Conversion of (1R,2R)-1-hydroxy-N-methyl-1-phenyl-2-propanaminium (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oate into (+)-sclareolide

To a suspension of 199.1 g of (1R,2R)-1-hydroxy-N-methyl-1-phenyl-2-propanaminium (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oate in 550 g of toluene were added dropwise, at T = 20-5°C and over 30 minutes, 230 g of 10% aqueous sulphuric acid. The reaction mixture was heated to 50°C and, after the removal of the aqueous phase, the organic layer was washed twice with 50 ml of water.

To the toluene phase, containing the free (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid, were added 6.9 g of acetic acid and the reaction mixture was heated at reflux for 2.75 hours, using a Dean-Stark trap to remove water azeotropically. At the end of the reflux period, the reaction mixture was cooled to approximately 50°C, washed with 100 ml of water and then with 100 ml of 3% aqueous $NaHCO_3$. It was thus obtained an organic phase which, after evaporation of the solvent, provided 113.6 g (91% yield) of (+)-sclareolide having a purity > 98% and an e.e. = 99%, purity and e.e. being obtained by chiral GC.

## Claims

1. A process for the isolation of (+)-sclareolide from sclareolide, characterized in that said process comprises the following reaction steps:

a) the hydrolysis of sclareolide into a corresponding hydroxy derivative,

b) treating, in a solvent, the hydroxy derivative with a pseudoephedrine enantiomer in order to obtain a biphasic system, wherein each phase comprises a majority of one enantiomer of the hydroxy derivative, and

c) treating the phase comprising a majority of the hydroxy derivative (8R)-8-hydroxy-13,14,15,16-tetranorlabdan-12-oic acid in order to convert the latter into (+)-sclareolide.

2. A process according to claim 1, wherein the solvent is an aromatic solvent, a petroleum fraction, a halogenated solvent, an ethers, an ester $C_4$-$C_{10}$ alcohols or mixtures thereof.

3. A process according to claim 2, wherein the solvent is selected from the group consisting of anhydrous tetrahydrofuran, toluene, xylene, benzene or cyclohexane.

4. A process according to claim 1, wherein the pseudoephedrine enantiomer is the (1R,2R)-2-(methylamino)-1-phenyl-1-propanol.

5. A process according to claim 4, wherein the pseudoephedrine enantiomer has an enantiomeric excess higher than 95%.

6. Use of a pseudoephedrine enantiomer for the optical resolution of sclareolide.

## Abstract

The present invention relates to the field of organic synthesis and more particularly to a new process to obtain (+)-sclareolide, starting from the racemic sclareolide. Said process is characterized by an enantiomeric or optical resolution using, as resolving agent, an enantiomer of the 2-(methylamino)-1-phenyl-1-propanol, also known as pseudoephedrine.